Fluvoxamine: Clinical Trials and Clinical Use

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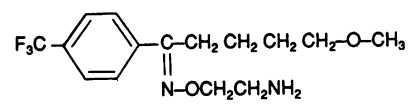
This paper reviews the clinical trials on the antidepressant properties of fluvoxamine and gives some guidelines on its clinical use. Other indications, such as its use in obsessive compulsive disorder and anxiety disorders are mentioned but not reviewed in detail.

Fluvoxamine maleate was synthesized by Duphar in 1971. It is a highly specific serotonin reuptake blocker which inhibits the presynaptic reuptake of 5HT. It does not block 5HT receptors. It has been extensively tested in a wide range of clinical trials which throughout the world, have now involved over 25,000 patients.

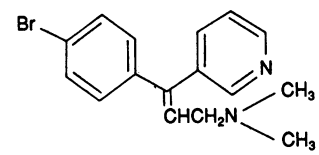
Fluvoxamine was first registered in Switzerland in 1983 and is now available in 27 countries throughout the world. It has been available for prescription in the United Kingdom since 1986. The chemical structure of fluvoxamine is totally different from tricyclic and second generation antidepressants. Fluvoxamine is a white, odorless, crystalline powder which has local irritant properties, and for this reason, it cannot be used parenterally. Its chemical name is 5-methoxy-4-(trifluoromethyl) valerophenone (E)-0-(2-aminoethyl) oxime maleate, and the molecular structure can be seen in Figure 1.

Fluvoxamine Pharmacology in Man

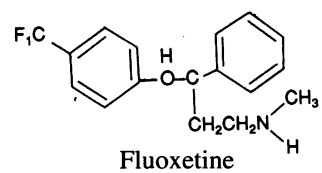
The mean plasma half-life of fluvoxamine is 15 hours. Oral administration of a single 100 mg dose to healthy volunteers produced maximum plasma levels (31-87 ng-ml) after 1.5 to 8 hours (de Bree 1984). Chronic administration reduces clearance, and increases elimination half-life to 17 to 22 hours. Steady state levels of fluvoxamine are attained within about 10 days. These kinetics apply to healthy volunteers, depressed patients and the elderly (Benfield 1986). Unlike fluoxetine, fluvoxamine does not appear to have any active metabolites, and certainly for the two primary metabolites, the absence of pharmacological effect has been established.



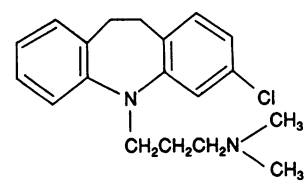
Fluvoxamine



Zimelidine



Fluoxetine



Clomipramine

Fig. 1: Chemical structures of the specific 5-HT reuptake inhibitors fluvoxamine, zimelidine and fluoxetine and the tricyclic anti-depressant clomipramine.

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Table 1 compares the effects of fluvoxamine with other antidepressants on radio-labelled neurotransmitter uptake into synaptisomes of rat brain. A powerful effect of fluvoxamine on 5HT systems is demonstrated. In healthy human volunteers, 150 mg of fluvoxamine daily causes a 50% decrease in platelet serotonin content confirming the strong effect on serotonin reuptake inhibition. Fluvoxamine does not possess significant anticholinergic activity and this is reflected in its side effect profile.

As with other antidepressants, fluvoxamine increases rapid eye movement (REM latency) and shortens total REM time by decreasing the number of REM sleep periods. It also produces a small reduction in the time taken to fall asleep.

Fluvoxamine has been compared with imipramine (Saletu 1983) and mianserin (Curran and Lader 1986) and been shown not to be associated with any significant impairment of psycho-motor activity in contrast to the other compounds.

Table 1
Effects of fluvoxamine and other antidepressants on radiolabelled neurotransmitter uptake into synaptosomes prepared from different regions(a) of rat brain (after Bradford 1984).

Concentration required to inhibit uptake by 50% (μmol/L)			
	5-HT	Noradrenaline	Dopamine
Clomipramine	0.8	4	15
Desipramine	12.5	0.12	40
Fluoxetine	1.3	16	32
Fluvoxamine	0.3	41	47
Zimelidine	8	50	79

(a) Cerebrum for serotonin uptake; hypothalamus for noradrenaline; corpus striatum for dopamine.

Therapeutic Trials in Depression

Fluvoxamine has been studied in open and blind trials, compared with placebo and with a variety of established antidepressants. Most comparisons have been with imipramine or clomipramine. Details of these studies are given in Tables 2 and 3.

Comparisons with Imipramine and Placebo

In a large multi-center study (Amin 1984) performed in 8 centres in North America and Europe, fluvoxamine was compared to imipramine and placebo in 464 patients with DSM-III major depression under double-blind conditions. Because of differences between the five North American centers and the three in Europe, only the North American data is presented here, which has been analyzed separately. The North American centers treated patients for 6 weeks compared with 4 in the European centers and there was much greater benzodiazepine prescribing in the latter groups. Pre-treatment comparability of the three treatment groups was high with regard to type and severity of depression, age and sex distribution. Mean pre-treatment HAM-D scores were 23.3 for fluvoxamine (n=110), 23.5 for imipramine (n=104), and 23.1 for placebo (n=106).

By the end of 2 weeks, fluvoxamine treated patients had shown a 37% improvement in HAM-D scores and this was significantly greater than imipramine or placebo. At the end of 4 weeks, the percentage of patients showing improvement with fluvoxamine was 52%, imipramine was 45% and placebo was 34%, and both fluvoxamine and imipramine were significantly superior to placebo. At the end of 6 weeks, percentage improvement had risen to 59% for fluvoxamine, 52% for imipramine and 32% for placebo. When the HAM-D was analyzed by factor scores (Guy 1976), Factor 1 (Anxiety/Somatization) and Factor 3 (Cognitive Disturbance) showed an earlier, statistically significant improvement over placebo in the fluvoxamine group versus imipramine.

When a HAM-D item analysis was carried out, fluvoxamine showed either greater improvement or more rapid onset of action in the depressed mood, suicidal ideation and somatic and psychic anxiety items. For depressed mood and suicidal ideation these differences were greater when those with initial high scores of 3 or 4 were studied separately. It would appear from this study that the overall antidepressant effect of fluvoxamine is equal to that of imipramine, but some aspects of the clinical syndrome respond more rapidly to fluvoxamine than to imipramine.

Other outcome measures show similar results. The Clinical Global Index (CGI) shows significant advantages for fluvoxamine over placebo at the end of week 2, and at the end of week 3 for imipramine over placebo.

Despite this clearly positive result, it should be noted that in two studies described in Table 2, fluvoxamine displayed low therapeutic efficacy (Dominguez et al 1985; Norton et al 1984). In both these studies, neither fluvoxamine nor imipramine were superior to placebo. In the Dominguez study, there was a very high placebo response rate of 50%. In contrast, in the Norton study the opposite effect occurred, with low response rates to treatment occurring in all 3 groups.

Comparisons with Clomipramine

Table 3 shows the results from three studies which compared fluvoxamine to clomipramine. Equivalent efficacy was apparent in all three studies.

Table 2
Summary of the results of comparative studies of fluvoxamine (F) and imipramine (I) and/or placebo (P) in depressed patients.

Reference	Patient Population (completing study)	Method of assessment[a]	Study design[b] and dosage	Duration (weeks)	Results	
					overall efficacy	side effects
Amin et al (1984)	351 inpatients and outpatients Major depressive disorder	HRS, CGI, SCL-90, BPRS, NOSIE, ZSR, DOTES	Db, r, p Titrated dosage 50 300 mg daily capsules	4	F ≈ I > P	Dizziness/syncope, dry mouth, sweating, tremor F < I Nausea, headache, anorexia F > I
Cassano & Conti (1984)	18 inpatients Major primary depression	HRS, CGI, SCL-90, BPRS	Db, r, p, pc Increased in fixed increments Mean finals F, 276 mg/day: P, 270 mg/ day capsules	4	F > P	Nausea/vomiting somnolence, hyperkinesia, sweating F > P
Dominguez et al (1985)	56 outpatients Moderate-marked primary depression	HRS, CGI, SCL-90	Db, r, p, pc Titrated dosage 100-300 mg daily capsules	4	F ≈ I ≈ P	Dry mouth, drowsiness (week 1) F < I Insomnia, nausea/ vomiting (week 1) F < I
Guy et al (1984)	36 inpatients Unipolar or bipolar primary depression	HRS, CGI, BPRS, NOSIE, ZSR, DOTES	Db, r, p Titrated dosage 50-300 mg nocte	4-6	F ≈ I	Dry mouth, tremor, constipation, dizziness F < I Headache, tachycardia F < I
Itil et al (1983)	34 outpatients Major primary depression	HRS, CGI, SCL-90 BDI, PMS	Db, r, p, pc Titrated dosage 50-300 mg daily capsules	4	F ≈ I > P	Anticholinergic F < I
Norton et al (1984)	83 outpatients Major depressive disorder	HRS, CGI, SCL-90, BPRS, DOTES, TWIS	Db, r, p, pc Titrated dosage Mean final: F, 133 mg/day: I, 153 mg/ day capsules	4	F ≈ I ≈ P	Dizziness/syncope, vasodilation, dry mouth, sweating F < I Anorexia, nausea/ vomiting, diarrhea, F > I
Poeldinger & Bures (1984)	20 inpatients Endogenous (8) Non-endogenous (10) Bipolar (2)	HRS, CGI	Db Titrated dosage 150-225 mg daily	4	F ≈ I	Few in either group

a Efficacy scales: Observer - BPRS = Brief Psychiatric Rating Scale; CGI = Clinicians' Global Impression; HRS = Hamilton Rating Scale; PMS = Profile of Mood States; NOSIE = Nurses' Observation Rating for Inpatients Evaluation. Patients - BDI = Back Depression Inventory; SCL-90 = Self-Report Symptoms Inventory; ZSR = Zung Self-Rating Depression Scale. Side effect assessment: DOTES = Dosage Record and Treatment Emergent Symptom Scale; TWIS = Treatment Emergent Symptoms Write-In Scale

b Db = double-blind; r = random; p = parallel group comparison; pc = placebo-controlled.

(Adapted from ADIS press, 1989)

Table 3
Summary of results of comparative studies of fluvoxamine (F) and clomipramine (C) in depressed patients.

Reference	Patient Population	Method of assessment[a]	Study design[b] and dosage	Results	
				overall efficacy	side effects
Coleman & Block (1982)	62 inpatients Unipolar or bipolar	HRS, CGI, self ratings	Db Fixed dosage 150 mg/day or titrated dosage 100-150 mg/day or 150-300 mg/day	F ≈ C	1 or more anticholinergic symptoms F < C
Dick & Ferrero (1983)	30 inpatients Marked severe depression	HRS, CGI self ratings	Db, r, p 50 mg tid capsules F < C	F ≈ C	Anticholinergic and digestive symptoms F < C
Klok et al (1981)	28 inpatients Endogenous	HRS, CGI, ZSR, LS	Db, r, p 50 mg tid capsules	F ≈ C	Anticholinergic F < C Central F ≈ C Gastrointestinal F> C

a Efficacy scales: Observer - CGI = Clinicians' Global Impression Scale; HRS = Hamilton Rating Scale; LS = Leyden Scale.
Patients - ZSR = Zung Self-Rating Depression Scale.
b Db = double-blind; r = random; p = parallel group comparison
(Adapted from ADIS press, 1989)

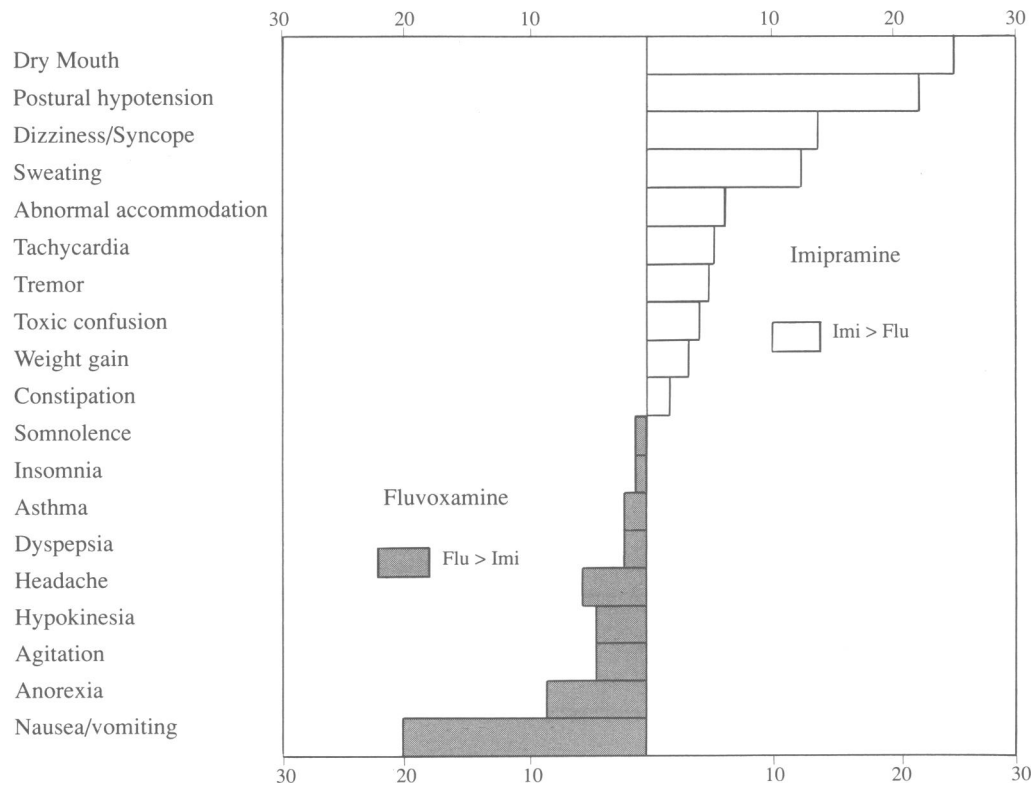

Fig. 2: Placebo corrected treatment emergent signs and symptoms.

Adverse Effects

The adverse effect profile for fluvoxamine is similar to that of other serotonin reuptake blockers. Table 4 shows the most frequent reported treatment related signs and symptoms in placebo-controlled studies, comparing fluvoxamine and imipramine.

Gastrointestinal symptoms appear to occur more frequently with fluvoxamine, with nausea or vomiting reported in approximately one third of patients. Clinically, my experience is that when this reaction does occur, it happens quickly, within the first 24 to 48 hours of treatment. It is usually mild or moderate and subsides after a few days. If the nausea or vomiting is marked, the drug may have to be discontinued. It is clearly important to inform the patient about this symptom. It is to some extent dose-related, but can occur even with a starting dose of 50 mg. It has been suggested that taking fluvoxamine with food helps to minimize this complaint. Other symptoms which are complained more of by fluvoxamine-treated patients are somnolence, constipation, agitation, anorexia, tremor, hypokinesia and asthenia, but only when compared with placebo base rates. Anticholinergic effects such as dry mouth, tachycardia, and difficulty in accommodation occur more frequently with imipramine treated patients, as do weight gain, tremor, sweating, dizziness and postural hypotension.

Figure 2 compares the side effect profile of imipramine and fluvoxamine for treatment emergent signs and symptoms (TESS), corrected for the corresponding rates attributed to placebo.

Changes in Vital Signs

Fluvoxamine does not appear to cause postural hypotension. The only changes observed are a small, probably clinically unimportant reduction in heart rate (Roos and Sharp, 1984). It would appear that fluvoxamine is remarkably free from cardiac toxicity.

Rare Side Effects

Because fluvoxamine has been marketed widely in Europe over a number of years, and the estimated treated population is now over 2,000,000 patients, it has been possible to build up a data base of rare side effects occurring in ordinary clinical practice. Only two types of events seem to have emerged, and these resulted in warnings being placed in the data accompanying the drug package. A small number of reports of raised liver enzymes have occurred. The rate appears to be low (1 : 50,000 treated patients) and, in all cases, changes have returned to normal when the drug has been discontinued. Occasional epileptic fits have been reported (incidence 1 : 50,000) during fluvoxamine treatment. Although there is no definite evidence of pro-convulsive properties for fluvoxamine, and one study (de Barsy, 1990) showed that fluvoxamine could be successfully and safely used in depressed epileptic patients, caution is recommended when using the drug with epilepsy.

Fluvoxamine in Overdose

Ten patients have died by drug overdose while taking fluvoxamine. In all cases, patients have taken multiple drugs, including fluvoxamine. No deaths have been reported by fluvoxamine overdose alone, even after ingesting up to 9 g of drug (30 times the recommended daily dose).

Table 4
The most frequently reported treatment-related signs and symptoms in placebo-controlled studies comparing fluvoxamine and imipramine.

Symptoms	Incidence of treatment-related signs and symptoms (% of patients)		
	Fluvoxamine	Imipramine	Placebo
Nausea/vomiting	37	17	11
Somnolence	26	25	9
Dry mouth	26	51	26
Headache	22	17	19
Constipation	18	20	7
Agitation	16	12	8
Anorexia	15	7	6
Insomnia	15	14	10
Dizziness/syncope	14	27	10
Sweating	11	23	13
Tremor	1	16	5
Hypokinesia	8	4	4
Asthenia	7	5	9
Abnormal accommodation	6	12	6
Diarrhea	6	2	6
Pain	6	2	4
Paraesthesia	5	5	4
Dyspepsia	4	2	1
Weight gain	4	8	5
Weight loss	4	5	5

Fluvoxamine Treatment in Particular Clinical Situations

There has been much renewed interest in the role of 5HT systems in suicide and suicidal ideation, with evidence showing that suicide is more frequent among depressed patients who have abnormal 5-HIAA in their cerebrospinal fluid, and that such patients may choose more violent means of suicide than those with normal brain 5HT function. Evidence from a number of different trials suggest that fluvoxamine has more powerful effects on reducing suicidal

ideation than imipramine. Wakelin and Coleman (1986) have reported that differences are particularly noticeable in those patients who are considered to be high suicidal risks. I am not aware of any reports of paradoxical reactions where impulsivity, suicidal ideation or aggression has been increased during fluvoxamine treatment.

Patients with Particularly Somatic Complaints

In the large multi-center trial by Amin (1984), fluvoxamine but not imipramine produced significant improvements in Factor 1 of the Hamilton Depression Rating Scale, which includes gastrointestinal and general somatic symptoms. This may have some clinical relevance when treating patients who have marked somatic symptoms.

Use in Patients with Obsessive Compulsive Disorder and Panic Disorder

Reviews of these areas are outwith the scope of this article, but there is now impressive data on the antiobsessional properties of fluvoxamine. Similarly, there is evidence from controlled trials that fluvoxamine has marked anti-panic properties.

Clinical Guidelines for Prescribing

Fluvoxamine can be given in a single daily dose, or in divided doses. The starting dose can be as low as 50 mg daily, and the dose then gradually increased to between 150 and 300 mg daily. A starting dose of 50 mg should help reduce the marked nausea that can occur with an initial dose of 100 to 150 mg at the start of treatment. The best regime appears to be a single evening dose, which causes fewer side effects. Patients should be told to swallow their tablets whole with water and preferably taken with some food. Fluvoxamine has the advantage over fluoxetine of a much shorter half-life; although the two drugs have not been directly compared in a clinical trial, they are clearly very similar in most respects. I have used both drugs extensively. Fluvoxamine may cause slightly more nausea in the short term, but with both drugs nausea does not seem to be a problem after the first few days. Fluvoxamine appears to cause less sleep disturbance and to be less activating and stimulating than fluoxetine. Its shorter half-life means that treatment changes are more easily made, particularly when a switch is being made to a monoamine oxidase inhibitor.

Fluvoxamine warrants a place as a drug of first choice in the treatment of major depressive episodes. It may be particularly appropriate in patients with marked suicidal ideation, patients who are overweight or who fear weight gain with other antidepressants, patients with marked somatic symptoms associated with depression, and particularly with patients where a lack of any sedative effect is required, so that patients can continue working and/or driving.

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